# ANNUAL REPORT

OF

# THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

AT THE

MASSACHUSETTS EYE AND EAR INFIRMARY

1963

243 CHARLES STREET
BOSTON, MASSACHUSETTS

## STAFF

David G. Cogan, M.D.: *Professor of Ophthalmology — Director*
W. Morton Grant, M.D.: *Associate Professor of Ophthalmology*
Jin H. Kinoshita, Ph.D.: *Assistant Professor of Biological Chemistry*
David D. Donaldson, M.D.: *Assistant Professor of Ophthalmology*
Toichiro Kuwabara, M.D.: *Assistant Professor of Ophthalmology*
Carl Kupfer, M.D.: *Assistant Professor of Ophthalmology*
Sidney Futterman, Ph.D.: *Associate in Biological Chemistry*
John S. Andrews, Jr., Ph.D.: *Instructor in Ophthalmic Research*
Masando Hayashi, M.D.: *Instructor in Ophthalmic Research*
Abraham Spector, Ph.D.: *Instructor in Ophthalmic Research*
Ephraim Friedman, M.D.: *Assistant in Ophthalmology*
Michio Oikawa, M.D.: *Research Associate in Ophthalmology*
Lawrence Stark, M.D.: *Research Associate in Ophthalmology*
Selma Hayman, Ph.D.: *Research Fellow in Ophthalmology*
Lorenzo O. Merola, B.S.: *Technical Associate*
Charles Snyder: *Librarian*

## TEMPORARILY ATTACHED TO THE LABORATORY

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James H. Elliott, M.D.: *Special Fellowship, USPHS*
Stephen J. Fricker, M.D.: *Fellow in Ophthalmology, USPHS*
George E. Garcia, M.D.: *Fellow in Ophthalmology, USPHS*
Jack E. Goldstein, M.D., *Special Fellowship, USPHS*
Arnold J. Kroll, M.D.: *Resident, Massachusetts Eye and Ear Infirmary*
Howard Leibowitz, M.D.: *Fellow in Ophthalmology, USPHS*
Simmons Lessell, M.D.: *Fellow in Ophthalmology, USPHS*
Ernst J. Meyer, M.D.: *Fellow in Ophthalmology, USPHS*
H. T. James Mount, M.D.: *Fellow in Ophthalmology*
Robert A. Petersen, M.D.: *Fellow in Ophthalmology, USPHS*
Robert D. Reinecke, M.D.: *Resident, Massachusetts Eye and Ear Infirmary*
Richard A. Thoft, M.D.: *Fellow in Ophthalmology, USPHS*

An Annual Report is the inventory of a year's accomplishment. But it generally reflects only those activities which have yielded positive results and gives no indication of the many failures and frustrations that, as any investigator knows, constitute the bulk of original research. If in the subsequent paragraphs it appears that well designed investigations have invariably led to clean results of a conclusive nature, that would be a simplification which we might wish to be true — but is not. Nor does the Report do justice to the diverse activities of the investigators who along with their researches here recorded are involved in a multitude of teaching, writing, miscellaneous discussions, preparation of grant applications and reports, and, of course, the banal housework of keeping a laboratory in shape. That which emerges in the form of positive results and constitutes an Annual Report is merely the visible part of the proverbial iceberg.

## Research

*Electron Microscopy.* Under the deft guidance of Dr. Kuwabara electron microscopy has flourished in the Howe Laboratory and now constitutes one of the major lines of investigation. The large 'scope which was installed several years ago at a cost of approximately $50,000 has been kept so busy that a second instrument had to be obtained, an acquisition made possible this year by a generous gift from the Concordia Foundation. This smaller machine, costing approximately $20,000, will be used for scanning purposes. The cost of installation, plus expensive upkeep means that these are major investments and ones which we are not taking lightly. We feel certain that electron microscopy will continue to yield a rich harvest of information of immediate interest to the histologist and biochemist and of potential benefit to the clinician and patient. To give some indication of the place of electron microscopy in medical research today it may be useful to record that the electron microscopes now in the Howe Laboratory are two of the thirteen currently in operation in the Massachusetts General and Eye and Ear Infirmary complex.

Dr. Kuwabara's primary concern of the past year has been the study of neuronal-glial relationships in the retina at the ultrastructural level. The metabolic and neurophysiologic studies carried out in the Howe Laboratory and elsewhere over the past several years have indicated that, contrary to earlier concepts, glia contributes considerably more to retinal function than simple mechanical support. The glia has been shown to synthesize and store the nutritive substances on which the neurones of the retina depend. The possibility exists that it actually participates in nervous integration within the retina. The anatomic evidences of this are being vigorously explored by electron microscopy.

Another subject studied with the electron microscope has been the ultrastructure of tumors in and about the eye. This investigation, headed by Dr. Arnold Kroll, has so far been concerned mainly with rhabdomyosarcomas of the orbit and melanomas of the choroid. In the rhabdomyosarcomas some of the tumor cells have been found to have heterogeneously arranged striae similar to embryonic skeletal muscle. In the melanomas a great diversity in cell types has been found, some cells having an abundance of mitochondria and other cells having an abundance of endoplasmic reticulum. In the words of one observer, some of these cells look as though they had a lot of energy and no place to go (those loaded with mitochondria) whereas other cells look as though they were doing a lot of work but had little energy (those containing abundant endoplasmic reticulum). In this paradox lies the secret of cancer. It is hoped that studies such as this may lead not only to a better classification of malignancies within the eye but to better understanding of the basis of cancer itself.

Although it is too early to warrant reporting results it may be noted that Dr. Kuwabara has begun the study of a large number of kidney biopsies from patients with diabetes, with the aim of discovering common denominators between the retinal and renal manifestations of this disease.

*Glaucoma Research.* Under Dr. Grant's supervision, experimental and clinical research on glaucoma continue advantageously combined. The Massachusetts Eye and Ear Infirmary's Glaucoma Consultation Service, which developed several years ago as a natural outgrowth of investigational work in the Howe Laboratory, continues in close affiliation with the Laboratory and provides excellent opportunity for extension of research from the fundamentals of the laboratory to the practical applications of the clinic. Funds for research on glaucoma which are supervised by Dr. Grant support work simultaneously in the Howe Laboratory and in the Glaucoma Consultation Service. Research Fellows supported by these funds have worked in the Howe Laboratory or in the Glaucoma Consultation Service according to the nature of their interests, the nature of the particular problems under investigation, and the space available. Glaucoma Fellowships this year have been held by Dr.

Jose D. Peczon, Dr. Claiborne G. Whitworth, and Dr. Vicente L. Jocson.

New research completed this year, carried out principally by Glaucoma Research Fellows and Ophthalmic Residents, has included: 1) clinical evaluation of digitalis in treatment of glaucoma; 2) investigation of dangers in the use of cardiac vasodilators in glaucoma; 3) study of drugs having a sedative effect and drugs having a stimulating effect to evaluate their influence on the intraocular pressure in glaucomatous patients; 4) examination of the effects of locally applied corticosteroid drugs in relation to intraocular pressure and corticosteroid glaucoma; and 5) assessment of the effectiveness of intravenous mannitol in emergency lowering of intraocular pressure.

These studies were all concerned with the very practical and important matter of learning what influences the intraocular pressure in glaucomatous patients, so that we may better know what may be used to the patient's advantage, as well as what should be avoided. The principal conclusions from these particular studies have been: 1) digitalization provides little or no improvement in control of glaucoma in patients already under intensive standard treatment; 2) vasodilators such as nitroglycerin and pentaerythritol tetranitrate, which are used to control attacks of pain from coronary artery disease, can be used in the presence of glaucoma without danger to the eye; 3) influence of sedative, tranquilizer, anticonvulsant or stimulant drugs on intraocular pressure in glaucoma is slight and inconstant, offering little in practical treatment and raising again the intriguing question of how much does state of mind influence pressure in glaucoma; 4) corticosteroids (substances related to cortisone) applied daily to the eye certainly can raise intraocular pressure, as well as induce mydriasis and ptosis; these findings are in support of an increasing number of investigational reports and clinical experiences indicating that corticosteroid glaucoma constitutes an important peril which must be recognized and guarded against; 5) mannitol administered intravenously is a very effective, well-tolerated osmotic agent for lowering intraocular pressure in preparation for surgery in glaucoma, corroborating what has been reported by others.

Certain continuing research projects carried on for a number of years by Dr. Grant are long-term systematic studies still in progress. Such projects include: 1) clinical and experimental studies of glaucoma in infants and children; 2) functional measurements on the aqueous outflow channels of normal and glaucomatous human eyes;

3) comparison of calibration data for Schiotz and applanation tonometers in sitting and recumbent positions; and 4) compilation in special punch-card form of the vast amount of information constantly accumulating on glaucomatous patients.

New research in progress at the end of the year included: 1) a combined functional and anatomical, laboratory and clinical investigation of blood vessels of the anterior segment of normal and glaucomatous eyes by Drs. Jocson, Peczon and Grant; and 2) an evaluation of the penetrability of hyaluronidase into the eye from the surface, by Drs. Jocson and Grant. This latter investigation was instigated by Dr. Grant's observations on obstruction of aqueous outflow channels by vitreous, and relief of this obstruction in excised eyes by hyaluronidase placed directly in the anterior chamber.

*Biochemistry and Cataracts* There is little doubt that the study of sugar metabolism in the lens by Dr. Kinoshita and his group is a major contribution to the elucidation of the cause of one type of cataract. In the case of galactose cataract metabolic reduction of sugar aldehyde in the lens produces a sugar alcohol which is trapped and accumulated in the lens fibers. The excess sugar alcohol causes osmotic swelling of the lens, and this constitutes the initial stage of cataract formation. Using galactose cataracts as an experimental model, Dr. Kinoshita, together with Mr. Merola, has found that the conditions in the lens are peculiarly favorable for the production of sugar alcohols. Galactokinase, the enzyme which phosphorylates galactose, is present in such low concentration that when abnormally high levels of galactose are made available to the lens, the excess is not readily metabolized in the usual way, through glycolysis. Instead the excess galactose is reduced to dulcitol by the enzyme aldose reductase. At the same time, there is an active hexose monophosphate shunt mechanism in the lens which supplies the TPNH essential for the reduction of galactose to dulcitol. Thus, in the lens low galactokinase activity in the presence of relatively high activities of the shunt mechanism and of aldose reductase provides a combination of factors favoring synthesis of sugar alcohol.

Dr. Hayman has purified the key enzyme, aldose reductase, from calf lens. The study of its properties after isolation revealed that aldose reductase has the interesting characteristic of converting sugar to sugar alcohol only when the sugar is present in high concentration. In an investigation of possible inhibitors of the enzyme, which might conceivably have therapeutic application, acetoacetate and other keto acids were found to be particularly effective. This may explain why a high fat diet, which contains these inhibitory substances, has been found (by others) to delay the development of galactose cataract. Lens aldose reductase has been found to react not only with galactose but also with a number of other aldoses. However, reactivity with galactose was higher than with other hexoses such as glucose and mannose. These findings provide an explanation for the fact that galactose produces greater osmotic effect than other sugars during incubation of rabbit lens. The highest level of sugar alcohol and the largest increase in water content occur in lenses incubated in the presence of galactose. On the other hand, only a slight increase in water is observed in the presence of mannose, which is most slowly reduced and provides the smallest accumulation of sugar alcohol. Glucose is intermediate between galactose and mannose in reactivity and in causing accumulation of sugar alcohol and water. Cataract is most readily induced by galactose, and less readily by glucose. These observations support Dr. Kinoshita's hypothesis that sugar cataracts are produced by movement of water into the lens in a response to hypertonicity created by accumulation of sugar alcohols.

Another form of cataract under study is that resulting from microwave radiation. Dr. Russell L. Carpenter of Tufts College is irradiating the rabbits and is supplying us with lenses at different times after exposure. One of the major changes found in these lenses is an increase in sodium and a decrease in potassium. This alteration in the cation distribution is accompanied by an increase in water in the lens. The suggestion emerging from these studies of experimental cortical cataracts, galactose and microwave, is that an osmotic change may be a common denominator. The increase in hydration of the lens may occur by either of two mechanisms: 1) an excess formation and accumulation of abnormal products of metabolism, or 2) a slowing of the cation pump mechanism that normally excludes sodium from the lens.

After cataract formation is initiated by osmotic disequilibrium, the second stage in opacification of the lens entails denaturation of protein. In this connection, Dr. Spector is continuing his efforts to fractionate lens protein. He has found that the soluble protein contains ten or more components, and each of these components in turn consists of aggregates of smaller units which may be dissociated from each other by urea. Possibly a pathologic disruption of this normal array of protein aggregates may be responsible for the irreversible stage of opacification of the lens in certain types of cataract.

A series of experiments to produce hypoparathyroid cataracts in rats was undertaken during the last few months of the past year by Dr. Richard Thoft. The problem heretofore has been to maintain animals alive sufficiently long in the hypoparathyroid state to permit the development of cataracts. Should this succeed — and at the moment it looks promising — we shall have a third type of experimental cataract available for biochemical study of its pathogenesis.

*Neuro-opthalmology and neurophysiology* Research on normal and abnormal processes of seeing have long occupied a prominent position in the Howe Laboratory's activities but this past year these researches have covered a wider range of activities than ever before.

On the biochemical side Drs. Futterman and Andrews have studied the esterification of vitamin A aldehyde. In the process of light adaptation in the retina this aldehyde (retinene) is released from the visual pigment by light. The vitamin A aldehyde is then reduced to vitamin A by TPNH. Following this, the vitamin A is esterified, or coupled, with fatty acids supplied by the retina. To study this step, a procedure has been developed for the isolation and analysis of retinal vitamin A esters. The fatty acid composition of these esters is strikingly different from that of the retinal lipids in general. Vitamin A esters synthesized by retinal tissue have been shown to be a mixture, the principal components of which are vitamin A palmitate, vitamin A palmitoleate, vitamin A stearate and vitamin A oleate. Together these components account for approximately 90% of the retinal vitamin A ester synthesized by the calf, sheep, rabbit, cat, frog and trout. These different species of animals appear all to employ the same enzymatic route for the synthesis of their retinal vitamin A esters. The next question, of whether in human retina the fatty acid composition of the vitamin A ester is the same as that in the animals, is now under investigation. The mechanism of vitamin A ester synthesis in the retina is also being studied.

On the histologic side Dr. Kuwabara and his collaborators have studied the structure of the glia by a number of tinctoral and histochemical methods (in addition to the electron microscopic method previously described). By the use of silver and gold impregnation Dr. Lessell has been able to delineate various types of retinal glial cells, partly corroborating and partly contradicting findings of other investigators. By other techniques various phosphatases have been localized in the retina. Perhaps most noteworthy is the finding of considerable activity of 5' -nucleotidase in the outer layers of the retina — noteworthy because no role has been ascribed to a phosphatase in this area — and the finding of strong ATPase activity in the ellipsoids of the rods and cones and at the sites of active transport. Alkaline phosphatase activity was also examined, and was found associated with capillary endothelium (but not that of Schlemm's canal) while acid phosphatase activity was found predominantly in the pigment epithelium.

Of neurophysiologic interest are Dr. Kupfer's observations on the connections between the eye and the lateral geniculate nucleus (LGN). A quantitative analysis has indicated that each optic nerve fiber innervates only one geniculate cell. Not only is this 1:1 ratio unique to the visual system but it permits a quantitative study of changes in the nerve cell (in this case, a geniculate cell) following sensory deprivation, i.e. interruption of the optic nerve fiber. In selected cases, it has been documented post-mortem that interruption of the optic pathways from the eye during life causes the cells of the LGN in man to decrease in size. The time course of this transneuronal atrophy has been followed from three months to over 50 years. Noteworthy was the absence of any change in the LGN other than decrease in cell size. An eventual decrease in the number of cells occurred only after a nine year period. Animal data has indicated that a decrease in the activity of several enzymes occurs concomitantly with decrease in cell size. Changes in the chemistry of denervated nerve cells are now being studied to determine their reversibility.

Also of neurophysiologic interest are: (1) Dr. Meyer's recording of eye movements by photoelectric means, a project undertaken in conjunction with Dr. Lawrence Stark of the Massachusetts Institute of Technology, and (2) Dr. Fricker's recording of light-stimulated signals from the brain. In his technique the eyes are exposed to flashes of light at specific frequencies. The signals are picked up by means of scalp electrodes over the occipital lobes, and are distinguished from other signals by original and sophisticated electronic circuitry. Both these projects are in a preliminary stage of exploration.

Along more purely clinical lines are the activities of Drs. Mount and Goldstein who, together with Dr. Cogan, have had the opportunity of studying a large number of patients with various neuro-ophthalmic disturbances. Of the several studies which were consummated this past year one was a study of intracranial aneurysms associated with opthalmoplegia, one a study (in conjunction with

Dr. Hugo Moser of the Neurology Department) of lipid emboli in the retinal arteries following arteriography, and another a study (in conjunction with Dr. Daniel Federman of the Medical Department) of a unique case showing retinal deposits in an unclassified type of reticuloendotheliosis. A series of patients was also reported by Dr. Cogan (Charles H. May Lecture) illustrating the little recognized syndrome of dissociated nystagums with posterior fossa disease.

*Histopathology* A very useful technique of isolating the retinal vessels by trypsin digestion of surrounding retina, which was originated several years ago by Dr. Kuwabara, continues to provide many new observations. Through liaison with pathology departments (particularly with that of Drs. Shields Warren and Merle Legg at the Deaconess Hospital) we have had the opportunity of examining several hundred diabetic retinas by this means. The results have regularly indicated shunt vessels as the prime feature of diabetic retinopathy with distension of capillaries and formation of microaneurysms as secondary phenomena.

This year approximately three hundred retinal vascular preparations from normal eyes were also studied, representing all ages from fetal life to senescence. The results of this survey, constituting a sort of normal life cycle of the retinal vasculature, were presented by Dr. Cogan as the Doyne Lecture at the Oxford Ophthalmological Congress.

Somewhat similar flat mounts of the choroidal vasculature have been prepared by Dr. Friedman. Several characteristics of vessels in the choroid differ from those of the retina. Those in the choroid show severe adventitial changes with age, a different type of hyalinization with hypertension, and an absence of characteristic angiopathy with diabetes.

In a conjoint histochemical study with Dr. Eugene Ciccarelli, Dr. Kuwabara investigated the corneal epithelium in a case of Meesman's dystrophy, corroborating a previous report of excessive glycogen within the epithelium but a new finding was made that intraepithelial cysts containing epithelial detritus are responsible for the characteristic vacuoles which are seen clinically with this disease.

*Instrumentation* Through the generosity of the Reisner Foundation and a supplement from the New England Ophthalmological Society we have obtained a TV camera and viewer which Dr. Donaldson will adapt for use as a clinical demonstrator. In the past, interesting patients could be examined only by a small number of individual doctors at a time. Now it is hoped that the use of closed-circuit television will permit collective viewing of external ocular lesions by a much larger group. This should facilitate conference demonstrations to the advantage of both the patient and audience.

*Miscellaneous activities* A curious syndrome characterized by interstitial keratitis and severe vestibulo-auditory symptoms has for many years been of special interest to us since it was first described from this Laboratory almost twenty years ago. A recent review of the literature failed to give conclusive indication of its cause but it was noted that several of the patients had a systemic disease suggestive of necrotizing vasculitis. One of our patients who recently succumbed to the disease showed a primary necrotizing aortitis, thus adding to the evidence that the eye and ear manifestations are part of systemic vascular disease. This case has now been studied in detail by Dr. Cogan and Dr. G. R. Dickersin (Pathology Department, Brockton Hospital). Some evidence suggests it may be a manifestation of rheumatic disease.

Transfer of certain electrolytes into lenses of living rabbits was studied by Drs. Garcia, Aaberg and Kupfer by the use of radioactive isotopes. They found that rubidium, which is a convenient analogue of potassium, moved into the lens more effectively than either sodium or phosphorous, thus confirming the thesis that the lens concentrates ions differentially.

The immunologic cause for rejection of corneal transplants is being investigated by Drs. Leibowitz and Elliott. It is generally accepted that many corneal transplants are not successful owing to an immunologic incompatibility between the donor cornea and the recipient host tissues. This type of immunologic response may be simulated in the rabbit cornea by utilizing soluble antigens. Various means are being explored to suppress this response.

Blackening of the cornea by the topical use of epinephrine was studied chemically and pathologically by Drs. Reincke and Kuwabara. Although this phenomenon is well known in the conjunctiva it has not previously been noted in the cornea. The pigment is believed to represent an oxidation product of the epinephrine.

The study of retinitis pigmentosa in the dog noted in previous Reports, has been progressing rather slowly because of breeding difficulties. The development of a pure and predictable strain of dogs with retinitis pigmentosa has not been accomplished as yet.

On the other hand a considerable number of eyes of animals which have been exposed to various toxic agents have been submitted to us for study. This is a project in which the toxicologic aspects are being conducted by Dr. Charles S. Delahunt, DVM, and the pathologic studies by Dr. Kuwabara.

Along with his duties as custodian of the rapidly expanding Howe Library, Mr. Charles Snyder writes or edits a series of articles that appear monthly in the Archives of Ophthalmology under the title "Our Ophthalmic Heritage". He also prepares biannually an annotated Bibliography of the History of Ophthalmology.

## TEACHING AND TRAINING

Through its staff the Howe Laboratory has for many years been deeply involved in Harvard teaching at both the undergraduate and postgraduate levels. This includes the lectures in pathology, physiology and pharmacology for the undergraduate students and much of the teaching in biochemistry, pharmacology and neuroanatomy in the postgraduate course. At present the undergraduate curriculum at Harvard is being reorganized, and Dr. Alfred Scott of the Infirmary's staff is representing ophthalmology. Our aim is to give students more awareness of the eye and its diseases than has been possible up to now. In the meantime the postgraduate course, under the leadership of Dr. Henry F. Allen, continues to be filled with its quota of able students who come to the Infirmary for a five months course prior to or following their residency training.

But it is with the training of the ophthalmic residents that the Howe Laboratory is most closely involved. Under the present system residents may choose either a three year or four year training period. In the latter case they spend the first year participating in some research project with the opportunity of becoming acquainted with the spirit and limitations of research. This program supported by the National Institutes of Health, and locally directed by Dr. Carl Kupfer, aims to provide opthalmologists of the future with an academic background. Lack of space is the present limitation for full expansion of the program.

The feasibility of programmed teaching of selected topics in ophthalmology is being explored by Dr. Reinecke in conjunction with the Harvard University Committee on Programmed Instruction.

## SERVICE ACTIVITIES

The scheduled appearance of an eclipse in mid-July caused a flurry of excitement in which the Howe Laboratory played a central role. The last large-scale viewing of an eclipse had caused no less than 170 cases of retinal burns (Australian eclipse, 1959) and many of these had occurred despite the use of filters that were commonly believed to be protective. Because of our past interest in radiation effects on the eye we were asked to draw up specifications for adequate protection of the eyes and make this information available to the public in practical terms. After surveying the actual experience and theoretical liabilities in eclipse viewing and correlating this with the meager experimental information available we concluded that developed photographic film having a light transmission equal to a #4 Wratten filter would be safe by a factor of at least 10. In practice we found such a filter could be simply and cheaply made by using fully exposed Xray film. Several thousand of such filters were distributed (gratis) by the Massachusetts Eye and Ear Infirmary and appropriate instructions were given in the newspapers and on the radio. We know of no casualties when these filters were used but their test in use was less than conclusive — as clouds obscured the eclipse.

One of the major accomplishments of the past year has been the establishment of a more effective system for obtaining eyes post-mortem. An enlightened public has increasingly expressed willingness to cooperate in making eyes available after death for corneal transplants and ophthalmic research. The difficulties in setting up an effective system for donations of eyes have been both legal and emotional. While the former has been partially rectified by expressed willing of one's eyes prior to death, the latter difficulty has been exaggerated in recent years by the requirements of special permits at the time of demise. We now have a revised autopsy protocol which makes less issue of special permits. Arrangements are being made that will, we believe, be easier for the next of kin and for the securing of eyes. We have been assured from many sources that the public is prepared and wants a more liberal policy for the donation of eyes after death, and we have obtained full cooperation from those involved in establishing such a policy.

A further service function of the past year was the preparation and delivery of testimony by Dr. Cogan before the Senate Subcommittee on Appropriations in behalf of the allocation of funds for ophthalmic research.

## Appointments, Special Lectures and Awards

Dr. Grant has completed his term on the Eye Study Section of the National Institutes of Health. Among his present appointments are: (1) Chairman of an ophthalmic advisory panel for the Food and Drug Administration relative to the Hazardous Substances Labeling Act; (2) Ophthalmic consultant to the U.S. Pharmacopeia and to the Council on Drugs of the American Medical Association; (3) Chairman of the Eye Pharmacy Committee of the Massachusetts Eye and Ear Infirmary; and (4) member of the Committee for Standardization of Tonometers, American Academy of Ophthalmology and Otolaryngology. We also note with undisguised pride the many favorable reviews of Dr. Grant's book "Toxicology of the Eye."

Dr. Kupfer has been appointed to the Research Training Committee of the National Institutes of Neurological Diseases and Blindness. Dr. Kinoshita and Dr. Futterman were chairman and vice chairman respectively of the Ophthalmic Biochemistry Conference for this past year.

Drs. Elliott and Futterman were given the Annual Fight for Sight citation this past year for their paper Tapetal Fluorescence and Night Vision in the Cat. This award is given for the best paper of the year presented at the meetings of the Association for Research in Ophthalmology.

Dr. Cogan was appointed the Henry Willard Williams Professor of Ophthalmology this past year. He also gave the Charles H. May Lecture (New York Academy of Medicine), the dedication addresses at the new John E. Weeks Laboratory (Portland, Oregon) and at the new department of ophthalmology at the University of Florida (Gainesville), and was awarded the Doyne Medal of the Oxford Ophthalmological Congress.

Dr. Donaldson has just completed a five week lecture tour of ten Central and South American cities under the auspices of the Pan American Association of Ophthalmology.

## Finances and Support

The Howe Laboratory has a great asset both in morale and material in the sustaining contributions received each year from a number of loyal physicians. Unfortunately the Laboratory has relatively little direct contact with patients who are in a position to make substantial contributions. We are therefore most grateful to those ophthalmologists and others who knowing the Laboratory's activities suggest this to potential donors as a suitable beneficiary. To maintain and expand the heavy program which is being conducted and contemplated in the Laboratory we need more uncommitted funds. Research on the eye is certainly one of the most vital of enterprises and one which can be deeply rewarding in a spiritual and philanthropic sense both for the investigator who does the work and for the benefactor who makes the work possible.

We owe our strongly felt thanks to the many who for one reason or another helped us this past year. We are grateful to the neighbors who contributed small funds in memory of a little blind boy; we are grateful for the large fund that enabled us to buy a second electron microscope; and we are grateful to all those listed below: individual benefactors, private foundations, and government agencies — all who have furthered the cause of ophthalmic research at the Howe Laboratory:

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Individual benefactors

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The Fight for Sight
  A study of retinitis pigmentosa in dogs
  Projection of the human retina on the lateral geniculate nucleus

Massachusetts Lions Eye Research Fund
  New construction

National Science Foundation
  Development of equipment for producing stereograms

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  Television demonstrator for clinical conferences

Research to Prevent Blindness, Inc.
- Eighth Conference on Biochemistry
- Studies on circulation of the retina

Alfred P. Sloan Foundation
- Basic experimental studies in glaucoma

U. S. Atomic Energy Commission
- The carbohydrate metabolism of ocular tissues

U. S. Public Health Service
- Ophthalmology Training Grants
- Electron microscopy of retinal dehydrogenases
- Metabolic histochemistry of the retina
- Pressure regulating mechanisms in glaucoma
- Research Career Development Award
- Experimental cataracts
- Lens protein and glutathione
- Lipid synthesis of non-adipose tissue
- Instrumentation in the field of ophthalmology
- Subjective color phenomena in normal and abnormal individuals
- Photographic recording of ophthalmic disease
- Development of anterior chamber angle in the human eye
- Control of intraocular pressure
- Retinal metabolism
- Projection of the human retina on the lateral geniculate nucleus
- Retinal microcirculation

In addition to staff and benefactors, the following secretaries, technicians, and assistants have contributed indispensably to the smooth functioning and successful operation of the Laboratory: Virginia C. Ayres, Inez M. Berry, Irene V. Brown, Lee Chumbley, Claude Delise, Elias Dikmak, Winifred J. Dornhoefer, M. Jean Garland, Jerome Glickman, Jeanne M. Grant, David M. Harrison, Phyllis A. Henri, Setsuko Hirosawa, Charles Horn, John F. Jope, Mary Klein, Elisabeth B. Lavoie, Irod Lindsay, Mona E. MacDonald, Frances Q. Mackenzie, Anna Marchurs, Gloria Merola, Sharon Mills, Setsuko S. Mimura, Charles Mokeler, Werner Mueller, Jr., Michael F. Norviel, Tomako Oishi, Patricia Palmer, David G. Perkins, E. Joann Perkins, Susan Pier, Wanda Pilarski, Peter Poulimenos, Mary L. Pruyn, James M. Rabb, Marjorie E. Saunders, Judith G. Schwerdt, Melvin J. States, Malcolm W. Swan, Bill Tung, Cynthia Vanden Burg, Thaddeus L. Wandel, Olga Wehm-Dalton, Suzanne M. Westerburg, Deborah Willard, Pao-Hsi Yeh, Billie-Louise G. Young.

David G. Cogan, M.D.
*Director*

# PUBLICATIONS

Christman, E. H.

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Editorial: Solar eclipse, 1963. J.A.M.A. *185*:38–39, July 6, 1963.

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The Stiles-Crawford effect in modern dress. *69*:285–286, March 1963.
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Friedman, E.

with Smith, T. R. and Kuwabara, T.: Senile choroidal vascular patterns and drusen. Arch. Ophthal. *69*:220–230, February 1963.

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Metabolism of the retina. III. The role of reduced triphosphopyridine nucleotide in the visual cycle. J. Biol. Chem. *238*:1145–1150, Mar. 1963.

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Experimental aqueous perfusion in enucleated human eyes. Arch. Ophthal. *69*:783–801, June 1963.

Fluorescein for applanation tonometry. Am. J. Ophthal. *55*:1252–1253, June 1963.

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Hayman, S.

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with Futterman, S., Satoh, K. and Merola, L. O.: Factors affecting the formation of sugar alcohols in ocular lens. Biochim. Biophys. Acta *74*:340–350, 1963.

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Kuwabara, T.

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Snyder, C.

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Inoculation — A lugubrious phase of ocular therapeutics. *ibid* *70*:726–728, November 1963.

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Spector, A.

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# LECTURES

Aaberg, T. M.

with Garcia, G. E.: Perfusion of the anterior chamber of the unanesthetized rabbit. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Andrews, J. S.

with Futterman, S.: Fatty acid composition of vitamin A ester of the calf retina. Eighth Conference on Ophthalmic Biochemistry, in Dedham, Massachusetts, February 22–24, 1963.

Biochemistry of ocular tissues. Series of lectures to the Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 10–23, 1963.

Cogan, D. G.

Diabetic retinopathy. V and VI Medical Services Grand Rounds, Boston City Hospital, in Boston, Massachusetts, January 30, 1963.

Diabetic retinopathy. Hartford Medical Society, in Hartford, Connecticut, February 4, 1963.

Nystagmus. House Officer Lecture, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, March 14, 1963.

Dissociated nystagmus with lesions in the posterior fossa. The Charles H. May Lecture, New York Academy of Medicine, Section of Ophthalmology, in New York, New York, March 18, 1963.

Diabetic retinopathy. Manhattan Eye, Ear and Throat Hospital, in New York, New York, March 19, 1963.

Pathology of diabetic retinopathy. Massachusetts Society of Internal Medicine, in Boston, Massachusetts, March 27, 1963.

Retinal involvement with a reticuloendotheliosis of an undetermined type. Alumni Association of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Lasers, masers, ultraviolet and infrared — effects on the eye. Harvard School of Public Health, Department of Industrial Hygiene, in Boston, Massachusetts, May 20, 1963.

Nystagmus. Massachusetts Medical Society, Ophthalmology and Otolaryngology Section, in Boston, Massachusetts, May 23, 1963.

A fatal case of the syndrome of nonsyphilitic interstitial keratitis and vestibulo-auditory symptoms. American Ophthalmological Society, in Hot Springs, Virginia, May 28, 1963.

Ocular pareses due to aneurysms at the circle of Willis. American Medical Association, Section on Ophthalmology, in Atlantic City, New Jersey, June 19, 1963.

Ocular motor dysmetria. Otological Research Unit, National Hospital, in London, England, July 4, 1963.

Development and senescence of the human retinal vasculature. The Doyne Memorial Lecture. Ophthalmological Society of the United Kingdom, in Oxford, England, July 8, 1963.

Oregon Ophthalmological Alumni Association, in Portland, Oregon, September 6, 1963.

1. Development and senescence of the retinal blood vessels.
2. Retinal angiopathy in diabetes.

with Kuwabara, T.: Pathogenesis of retinal microangiopathy. Symposium: The Microangiopathy of Diabetes. American Diabetes Association in Cherry Hill, New Jersey, October 24, 1963.

Radiation effects on the eye. American College of Physicians, Course in Environmental Medicine, in Boston, Massachusetts, December 10, 1963.

Ophthalmic pathology. Harvard Medical School, Second year class, in Boston, Massachusetts, December 13, 1963.

with Picard, E. H.: 13–15 Trisomy. New England Ophthalmological Society, in Boston, Massachusetts, December 18, 1963.

Donaldson, D. D.

Postgraduate Course in Ophthalmology, Harvard Medical School:
  Corneal dystrophy, January 14, 1963.
  Diseases of chamber angle, January 18, 1963.
  Systemic disease of anterior segments, January 24, 1963.
  Neuro-ophthalmic anatomy, September 24–October 11, 1963.

Ocular manifestations of syphilis. Dermatology Department, Massachusetts General Hospital, in Boston, Massachusetts, January 31, 1963.

Midwinter Seminar in Ophthalmology and Otolaryngology, University of Miami Medical School, in Miami, Florida, February 2–9, 1963.
  Confusing corneal lesions.
  The eye and systemic diseases.
  Gonioscopy as a means of diagnosis and treatment.
  Diagnostic problems in fundus lesions.

Problems in diagnosis and treatment of corneal dsytrophy and degeneration. Detroit Ophthalmological Society, in Detroit, Michigan, March 28, 1963.

Characteristic signs of systemic diseases in the eye. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 23, 1963.

Ocular signs of endocrine and metabolic disorders in the child. Pediatric Service, Massachusetts General Hospital, in Boston, Massachusetts, April 25, 1963.

Non-ionizing radiation with special reference to the eye. Industrial Hygiene Course, Harvard Medical School, in Boston, Massachusetts, May 20, 1963.

External diseases of the eye. Series of lectures to the Lancaster Courses in Ophthalmology, in Waterville, Maine, July 19–23, 1963.

Fundus findings in systemic disease. House Officer Lecture, Massachusetts Eye and Ear Infirmary, in Boston, Massachusets, July 25, 1963.

Gonioscopy. American Academy of Ophthalmology and Otolaryngology Glaucoma Course, in New York, N.Y., October 20–25, 1963.

Pan American Lectures, in Mexico City, Panama City, Lima, Santiago, Cordoba, Buenos Aires, Sao Paulo, Rio de Janeiro, Caracas, San Juan, October 29–December 4, 1963.

Corneal dystrophies and degenerations.
Conditions of the anterior chamber angle.
Unusual conditions of the fundus.

Postgraduate Course, State University of New York, College of Medicine, in Syracuse, New York, December 6–7, 1963.

Signs of systemic diseases in the anterior segment of the eye.
Tumors and cysts of the iris and ciliary body.
Diagnosis of fundus pathology.
Neuro-ophthalmic diagnosis in aneurysms and tumors.

Elliott, J.H.

Fluorescence in the tapetum of the cat's eye. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Friedman, E.

The ophthalmologist and the blind patient. Peripatology Students, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, March 28, 1963.

Retinal Circulation. House Officer Lectures, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 4 and October 1, 1963.

Retinal microcirculation in vivo. 11th Microcirculatory Conference, in Washington, D.C., April 8, 1963.

with Kuwabara, T. and Cogan, D. G.: Retinal microcirculation in vivo. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Retinal microcirculation in vivo. Association for Research in Ophthalmology, in Atlantic City, New Jersey, June 18, 1963.

Ophthalmology. Harvard Medical School, Third year class, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, October–November, 1963.

Retinal circulation. Surgical Conference, Beth Israel Hospital, in Boston, Massachusetts, October 28, 1963.

with Smith, T. R. Pathology. Postgraduate Course in Ophthalmology, Harvard Medical School in Boston, Massachusetts, November–December 1963.

Physiology of the eye. Series of lectures, Simmons College Orthoptics Course, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, November–December, 1963.

Retinal circulation. Board of Managers, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, December 4, 1963.

Futterman, S.

Co-Chairman. Eighth Conference on Ophthalmic Biochemistry, in Dedham, Massachusetts, February 22–24, 1963.

Biochemistry of ocular tissues. Series of lectures to the Postgraduate

Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 10–23, 1963.

GRANT, W. M.

New England Ophthalmological Society, in Boston, Massachusetts.
  Gonioscopy, January 16 and February 20, 1963.
  Applanation tonometry, January 16 and February 20, 1963.

Glaucoma. Department of Ophthalmology, Ophthalmic Graduate Course, Glaucoma Conference, Louisiana State University School of Medicine, in New Orleans, Louisiana, March 16–17, 1963.

Open-angle glaucoma associated with vitreous filling the anterior chamber. American Ophthalmological Society, in Hot Springs, Virginia, May 28, 1963.

Participant: National Institutes of Health Glaucoma Conference, in Hot Springs, Virginia, May 29–June 1, 1963.

Congenital glaucoma. House Officer Lecture, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, August 9, 1963.

Toxicology, tonometry and tonography. Series of lectures to the Lancaster Courses in Ophthalmology, in Waterville, Maine, August 22–23, 1963.

Department of Pharmacology, Harvard Medical School, Second year class, in Boston, Massachusetts.
  Laboratories, October 15, 22 and 29, 1963.
  Pharmacology of the eye, December 13, 1963.

Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts.
  Ophthalmic toxicology, November 1 and 6, 1963.
  Pathology of glaucoma, December 6, 1963.

HAYMAN, S.

with Kinoshita, J. H.: Lens aldose reductase. Federation of American Societies for Experimental Biology, in Atlantic City, New Jersey, April 20, 1963.

KINOSHITA, J. H.

Co-Chairman. Eighth Conference on Ophthalmic Biochemistry, in Dedham, Massachusetts, February 22–24, 1963.

Biochemistry of ocular tissues. Series of lectures to the Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 10–23, 1963.

KNOX, D. L.

Unusual ocular movements in a patient with myasthenia gravis. New England Ophthalmological Society, in Boston, Massachusetts, January 16, 1963.

KROLL, A. J.

with Kuwabara, T. and Howard, G. M.: Electron microscopy of rhabdomyosarcoma of the orbit. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Electron microscopy of rhabdomyosarcoma of the orbit. Association for Research in Ophthalmology, in Atlantic City, New Jersey, June 18, 1963.

Kupfer, C.

House Officer Lectures, Massachusetts Eye and Ear Infirmary.
  Outflow mechanisms, January 17, 1963.
  Control of outflow resistance, July 18, 1963.
  Neuro-ophthalmic studies, November 26, 1963.

Retinal ganglion cell degeneration following chiasmal lesions. Wilmer Meeting, The Johns Hopkins Hospital, in Baltimore, Maryland, April 26, 1963.

Participant. National Institutes of Health Glaucoma Conference, in Hot Springs, Virginia, May 29–June 1, 1963.

Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts.
  Electrophysiology, November 5, 1963.
  Physiology of aqueous humor, November 7–8, 1963.

Kuwabara, T.

Pathology of retinal vessels. Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, January 13, 1963.

Diabetic retinopathy. Endocrinology Conference, Massachusetts General Hospital, in Boston, Massachusetts.

with Ciccarelli, E.: Meesmann's dystrophy. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Horizontal cells. Ophthalmic Pathology Meeting, Armed Forces Institute of Pathology, in Washington, D.C., April 24, 1963.

Histochemistry of the retina. Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 17 and 19, 1963.

Lessell, S.

Silver carbonate studies of retinal histology. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Retinal phosphatase histochemistry. Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 1963.

Mount, H. T. J.

Instructional Course Ophthalmodynamometry, New England Ophthalmological Society, in Boston, Massachusetts, March 20 and April 23, 1963.

Alzheimer's disease and homonymous hemianopsia. Alumni Association

Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 22, 1963.

Snyder, C.:

A loathsome or dangerous disease — Trachoma and the Immigration Laws. New England Ophthalmological Society, in Boston, Massachusetts, April 23, 1963.

Spector, A.

Lens Proteins. Eighth Conference on Ophthalmic Biochemistry, in Dedham, Massachusetts, February 22–24, 1963.

Fractionation of calf lens proteins. Ophthalmology Research, Columbia University, in New York City, New York, May 14, 1963.

Biochemistry of ocular tissues. Series of lectures to the Postgraduate Course in Ophthalmology, Harvard Medical School, in Boston, Massachusetts, October 10–23, 1963.

## EXHIBIT

Donaldson, D. D.

The eye and systemic disease: Characteristic and pathognomonic ocular signs. American Academy of Ophthalmology and Otolaryngology, in New York, New York, October 20–25, 1963.

# FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

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TO BE APPLIED TO THE USES OF SAID LABORATORY.

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